Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

7441 '04 NOV 12 P1:30

November 11, 2004

Subject: **Docket No. 2004N-0355**: Scientific Considerations Related to Developing Follow-on Protein Products

Dear Dr. Galson:

Genentech, Inc. appreciates the opportunity to provide comments to the Docket on scientific topics related to the development of follow-on protein products. As you are aware, Genentech is a leading biotechnology company headquartered in South San Francisco, California. In the 28 years since our founding, we have discovered and introduced 13 significant therapies for serious and life-threatening diseases, including cancer and heart disease. Our record demonstrates that we have been in the forefront of scientific and technical developments, resulting in innovative, safe, and effective products using cutting-edge biotechnology processes.

We sincerely appreciate the Food and Drug Administration's (FDA) recognition that all relevant scientific issues should be discussed and considered before moving forward with developing a Draft Guidance document outlining a potential approval pathway for follow-on protein products (or "generic" biologics). Genentech applauds the FDA for responding to the biotechnology industry's request for a more inclusive public process and for holding a Stakeholder meeting in September. Only by engaging in an active discussion with all stakeholders can the FDA determine whether the development of a regulatory pathway for follow-on protein products is appropriate; and if so, the best direction and method for constructing such a pathway. Further, Genentech appreciates the FDA's commitment to convening a more in-depth scientific dialogue on the issue of follow-on protein products, and looks forward to the upcoming FDA/DIA Scientific Workshop that is scheduled for February 14–16, 2005. It is critical for the FDA to hear from a broad spectrum of scientific experts regarding the overall challenges in biotechnology development and manufacturing before moving forward with policy development in this complex area.

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We are also pleased that the FDA has prepared and intends to make public a document illustrating prior regulatory pathways for both natural source-derived and biotechnology-derived protein products that are currently on the market. How the FDA has viewed other protein products may provide insight into both the science of protein products and the regulatory pathways that the FDA has used in the past. It will also help elucidate the contours of what the FDA thinks it may use or disclose from the innovatory company's application as it reviews a second company's follow-on license application. Because we think this document has important bearing on the scientific issues related to follow-on protein products, we ask that the Agency file the upcoming document to this docket, and ask that the Agency extend the time allowed for comment to this docket for a minimum of 90 days after the document is made public.

While Genentech supports the current FDA process for seeking public input on the relevant scientific issues in question, we encourage the FDA also to seek public input on the myriad legal issues inherent in the development of an approval policy for follow-on protein products. We realize the focus of these comments is on specific scientific issues; however, we believe these issues are not severable from several important legal issues. As such, we strongly urge the FDA to commit to an equally robust public discussion regarding the treatment and use of confidential commercial and trade secret information before moving forward with developing and publishing a Draft Guidance document relating to follow-on protein products.

Moreover, there are many scientific issues that cannot be fully discussed or resolved without a clearer understanding of exactly what data and information from one company's application will be used or disclosed when the FDA reviews an application for a follow-on protein product. The degree to which the FDA will attempt to use the data in the application for the innovator's product during the review of the second application will have a direct and immediate impact on the scope of the data the second company will have to provide in order to prove that its product is safe, effective, and of high quality.

Our general comments, as well as specific comments to FDA's questions under each topic are provided below.

I. GENERAL COMMENTS

Although FDA often pairs natural source derived proteins and biotech protein products, our comments are limited to biotech protein products. Proteins are large molecules with intricate tertiary structures, frequently adorned with complex carbohydrate structures, and they often have multiple sites with diverse biological effects. Protein-based biopharmaceuticals (protein products) are typically manufactured by means of biological systems involving genetically engineered cells. Due to their complex nature, proteins readily change in composition and/or structure in response to their physicochemical environment either during production by cells in culture, during the multiple purification steps that follow, or during long-term storage and handling. Such structural changes can at times alter a protein's biological activity and consequently its therapeutic effectiveness and safety.

Furthermore, it is important to note that the larger and more complex protein products, in particular glycoproteins, are generally produced and purified not as single species but as entire families of related variants of the primary protein sequence and/or carbohydrate structure. Individual variant members of these families each have distinct but closely related structures and can sometimes exhibit significant differences in biological activities and potency, pharmacokinetic or pharmacodynamic behavior, and safety and effectiveness profiles. Because they are so closely related structurally, such product-related variants are often difficult to separate during the manufacturing process or even during analytical testing and characterization. Further, the proportions of these distinct structures can vary in response to their environment (e.g., during the biosynthetic phase in culture or during purification). As a result, the particular distribution of variants, i.e., the variant profile, for a particular protein product is a unique fingerprint reflecting that product's method of production and purification, its stability in the final formulation, and the analytical methods used for measurement. Even with the most sophisticated analytical techniques currently available, the complex variant profiles of protein products cannot always be teased apart completely into their distinct components. Depending on the analytical method used, subtle but potentially significant changes

in product-related variants or process-related impurities generated by the manufacturing process could go undetected.

In addition, the biological systems used for the production of protein products can contribute protein-based impurities of their own (host cell proteins) either released by the host cells themselves or comprised of the biologically derived growth factors used to culture those cells. These impurities have to be cleared to acceptable levels by the purification process to avert safety concerns for the patients. Furthermore, the cell culture and purification processes used to manufacture protein products generally contribute a variety of other large and small molecular weight impurities that also have to be cleared to acceptable levels from the final product. Effective clearance of such impurities by the manufacturing process must be established through well-designed validation studies since these impurities can be present but below detectable limits in the (often relatively dilute) final product.

Substrate and genetic consistency of each production cell line needs to be demonstrated; each process needs to be characterized and validated for consistency; and the unique safety and effectiveness profile for each product needs to be assessed in animal and human studies. Furthermore, since biotechnology-derived protein products are made from living organisms, a minor change to the manufacturing processes or respective controls used to make a particular product can have significant consequences on the composition or conformational make up—hence on the safety and effectiveness—of the products. The graph in Figure I.1 below demonstrates the impact of a process change that was implemented during the manufacture of one of Genentech's growth hormone products. The cause of the immunogenicity remains unclear today.

As a consequence of the above realities, the ultimate composition of a protein product, and the specifications for a safe and effective therapeutic cannot be determined by analytical testing and characterization of the product alone.

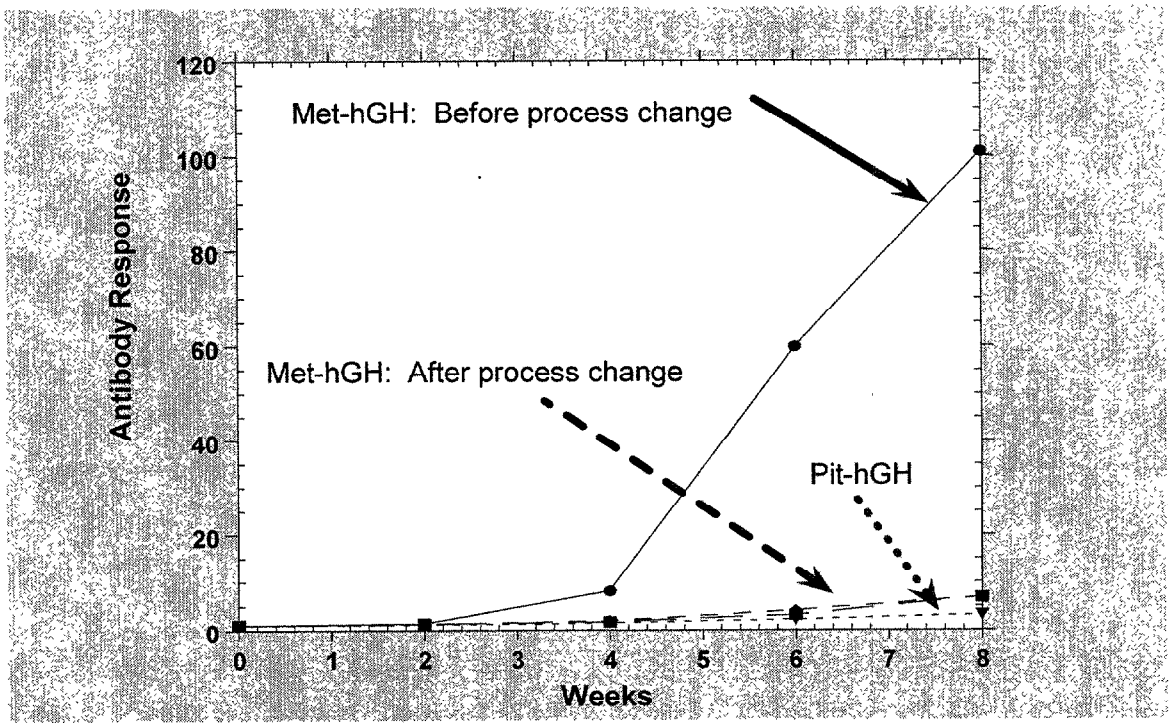
We agree that innovation is the key to a more rational and affordable drug development process. However, to ensure the safety and effectiveness of follow-on protein products, such products must be required to meet the same rigorous

approval standards applied by the FDA for the approval of an innovator's product. Unlike comparative capabilities that exist for small molecule products, Genentech does not believe that current scientific standards allow for reliance on analytical data and information generated from one biotechnology-derived product to support approval of a product manufactured using a different process.

For the reasons stated above and those fully outlined in our Specific Comments below, we remain unconvinced that the FDA could safely move forward with an abbreviated approval pathway similar—in either substance or spirit—to the ANDA pathway currently available for small molecule drugs approved under the Food, Drug, and Cosmetic Act. Unlike small molecules drugs, protein products are generally more difficult to characterize, and sufficient scientific tools are not currently available to determine the safety and effectiveness of follow-on protein products without reliance on extensive analytical information and animal and human studies.

Since the "pharmaceutical equivalence (sameness)" of small molecule products can be demonstrated unequivocally, the safety and effectiveness data collected by the innovator product is ultimately transferable to the generic product. In contrast, the safety and effectiveness data compiled regarding a biotechnologically derived protein product is inextricably linked to both the product and the manufacturing processes used to produce it. A manufacturer of a follow-on protein product will need to perform all of the process development and validation steps performed by an innovator since there is no opportunity for a follow-on manufacturer to compare their manufacturing process with the innovator's at a detailed level. Consequently, the manufacturer of a follow-on protein product may not identify the critical process parameters identified by the innovator as key for controlling a particular product characteristic or even develop an analytical test for that characteristic. With no currently available, scientifically established procedures for ensuring safety and effectiveness through purely analytical comparisons of two protein products, we believe manufacturers of follow-on protein products must be required to conduct and complete a full complement of critical animal and clinical studies to justify approval.

Figure I.1
Product Variation as a Result of Process Change



II. SPECIFIC COMMENTS

A. MANUFACTURING ISSUES

1. What aspects of the manufacturing process determine the characteristics of a protein product?

The following aspects of the manufacturing process determine the characteristics of a protein product that may or may not be discernable by analyzing the final product directly. Because all of these aspects of the manufacturing process are critical, all must be fully studied and documented in any application submitted by a manufacturer of a follow-on protein product:

1.1 Genealogy and characterization of the host cell line and vector system used.

These can impact both the genetic consistency during extended culture and the risk of potential biological contamination of the process. Choice of the host cell line and the vector determine the spectrum of relevant host cell proteins to be cleared as well as the characterization, in-process detection, and clearance requirements for endogenous viruses and adventitious agents.

1.2 Sequence of the gene of interest and verification for the protein product derived from the production cell line.

Confirmation at the end of production of the primary protein sequence as predicted by the sequence of the expressed gene is performed to avoid unintended sequence mutations.

1.3 Environmental conditions, cell growth and productivity, and duration of production culture incubation.

These aspects (i.e., the critical process parameters) of cell culture processes can often impact the extent of post-translational modifications (e.g., glycosylation), post-secretion degradation (e.g., proteolysis, deamidation), and release of retroviral particles and other host cell components into the harvested culture fluid for purification.

1.4 Mechanisms of separation, chromatography ligands, and specific conditions (critical process parameters) used in the purification process.

These aspects of purification processes often determine the spectrum of product-related variants and level of residual impurities present in the final product, i.e., they often determine the product profile.

1.5 Product hold times and conditions throughout the purification process.

Hold times and conditions at various stages of the purification process (including the harvested culture fluid, process intermediates, and the final purified bulk for storage) should be validated to avoid any adverse impact on the quality of the final product.

1.6 Raw materials used throughout cell culture and purification processes.

The raw materials specified for a process determine the likelihood of biological contamination, degree of impurity clearance required, and risk, if any, some materials might pose as residual impurities.

1.7 Extent of process validation.

Scientifically sound process validation studies should be conducted to determine acceptable ranges for critical process parameters, prevention of process contaminations, control of bioburden, and acceptable clearance of process impurities, endogenous viruses, and adventitious viruses.

1.8 Analytical methods, as well as associated reagents and standards (especially non-compendial) used to validate the manufacturing process, characterize the product, and provide for in-process controls.

Innovators invest tremendous resources to develop sensitive assays based on a thorough understanding of their manufacturing processes, such information and experience are not available to manufacturers of follow-on protein products. These analytical methods are often not applicable to follow-on protein products manufactured by a different process. Consequently, cross-validation of the methods developed by innovators and manufacturers of follow-on protein products is not appropriate.

2. What parts of the manufacturing process should the Agency focus on when assessing similarity between products?

When assessing the similarity between follow-on protein products manufactured by different companies by different means, particular attention should be paid to the following factors:

2.1 Common genealogy of the engineered host cells

The recombinant elements and expression vectors used in the construction of the engineered host cells used for production are typically tailored to each other and to the anticipated production requirements by the innovator. These can have a bearing on cell specific production rate, post-translational modification of the protein product, genetic consistency during long-term cell culture used for production, the extent of DNA clearance required, and the particular probes or methods to be used for measurement.

The biological tissue of origin and any biologically-derived growth factors used in the isolation and culture of the host cells and the production cell line derived from them have a bearing on the potential adventitious biological agents (e.g., bacteria, fungi, mycoplasma, viruses, prions) to which the cells may have been exposed or to which they could be susceptible during routine manufacturing. Consequently the model viruses used for clearance validation as well as the cell substrates used for the detection of any adventitious viral contaminants must be selected in the context of the host cell system to be used for production.

The endogenous retroviruses typically carried by the mammalian host cells, their extent of molecular characterization, and their known potential infectivity also have a bearing on the degree of viral clearance to be demonstrated by the manufacturing process and the types of in-process controls that would be required. Accumulated experience by the innovator with the same, well-characterized host cell/vector system used to manufacture multiple products with established safety records results in a high degree of confidence by the innovator in the consistency and safety of future protein products derived from it.

2.2 Raw materials

Any new raw materials introduced as a result of manufacturing changes should be assessed to ensure they do not present any additional safety risk to the product. If the raw materials present the potential for new sources of biological contamination to the manufacturing process, adequate controls should be put into place to avert this risk. If the raw materials are of a new class of impurities not represented by previous model molecules used in process validation, the effective clearance of such raw materials from the final product should be validated anew.

2.3 In-process controls and safeguards against contamination

When implementing manufacturing process changes, in-process controls should be maintained to ensure a comparable degree of monitoring and control of the process. By doing so the aim should be to ensure comparable or increased manufacturing consistency between batches. Also, any changes in manufacturing should maintain adequate and comparable safeguards against contamination, including environmental monitoring, cleaning, sterilization and operating procedures, raw material and in-process tests. Because in-process controls and safeguards are an integral aspect of the safety, effectiveness, and quality of any product, manufacturer of follow-on protein products should be expected to perform the same level of rigorous manufacturing as an innovator.

2.4 Performance of the manufacturing processes used

Changes in manufacturing processes must be assessed with respect to their potential impact on the quality of the product. For example, cell culture process changes should not alter the mixture of product-related variants and process impurities generated beyond the ability of the downstream purification process to deliver a consistent and comparable product profile and to clear the impurities from the product to an adequate degree. Similarly, changes to the purification process should also not compromise its ability to deliver a consistent and comparable product and to clear impurities from it adequately.

Scientifically sound validation of any process changes to demonstrate their ability to generate a comparable product under conditions of normal manufacturing variability is an important requirement. The ability to demonstrate statistically compelling

comparability of any manufacturing process following implementation of particular changes requires a significant historical base of manufacturing experience with the original process as well as the pre-clinical and clinical experience to determine the acceptable ranges of product and in-process specifications. Typically only the innovator, or its collaborating partner, has the available manufacturing, pre-clinical, and clinical history of the product to be able to demonstrate comparability of a changed manufacturing process. Because the FDA should not rely on the manufacturing data or other trade secret or confidential information it has received from the innovator, and since the manufacturing process of the follow-on company will be different from the innovator's manufacturing process, each follow-on manufacturer will have to create the same base of information on its product as an innovator does, so that the follow-on manufacturer can understand any changes it makes in its manufacturing over time.

2.5 Comparable analytical methods, critical reagents, and reference standards used for in-process control and product testing

When an innovator company establishes the comparability of the products resulting from slight changes in manufacturing processes, the particular methods used to test the product against release specifications or to monitor process intermediates for in-process control purposes should either be kept the same or be cross-validated to detect the same species of product-related variants or process-related impurities. Similarly, unique reagents, assay controls, and reference standards used to perform such analyses must be maintained constant or cross-validated for consistency. In some instances, for example in the case of a host-cell protein assay, the reagents necessary are unique to the host cell and manufacturing processes used.

Generally only the innovator, or its collaborating partner, has access to the historical reference standards, unique reagents, and specific assay protocols necessary to cross validate consistency between analytical methods. Because the follow-on manufacturer would not have access to this information, the follow-on manufacturer must do the same type of validation of its entire analytical methodology as was required by FDA for the analytical methods used for the innovator product.

B. CHARACTERIZATION

1. What is the capability of current analytical technology to adequately characterize protein products?

Current methods can be categorized as either "resolving" or "non-resolving" methods. Non-resolving methods—including certain spectroscopy (e.g., CD, UV/Vis/fluorescence), immunoassays, and NMR—do not have the necessary dynamic range or precision to be informative in comparative analyses. They provide only ensemble average data about a sample, and are inadequate to establish the full structure of a protein. They are also inadequate substitutes for bioassays for demonstrating the presence of the correct 3D structure for activity. As discussed in Item E below, potency results only reflect the aggregate properties of the total drug, not the properties of individual components (variants) in the drug. Whether the context is testing for the presence of low levels of structural alterations of the product or impurities, current analytical technology is insufficient: they suffer from the criticism that "the absence of evidence is not evidence of absence".
Thus, non-resolving methods are not useful for assessing the "sameness" of two preparations, especially if the process information is not available for one of the products.

Resolving methods—including chromatography, electrophoresis, and mass spectroscopy—provide very detailed information on structural and charge heterogeneity and are the main tools for process controls and product characterization. They add to the accumulation of knowledge about the process and product resulting in continuous improvement of characterization capability. This not only enables the identification of critical product quality attributes but also allows the identification of critical process parameters to ensure consistent drug manufacture. However, as depicted in Figure II.B.1.1, even some highly-resolving methods lack the power to fully characterize the heterogeneity of some protein products, and they always lack the ability to assess biological activities directly.

In addition, a follow-on manufacturer may not know what critical quality attributes to measure. As illustrated in Figure II.B.1.2, Glycoprotein A's clearance in humans depends on terminal GlcNAc, and not the results of the sialic acid content or IEF analysis that would be performed in a typical drug product analytical comparison.

This detailed information often is only in the hands of innovators, the identification of terminal GlcNAc as a key parameter controlling the clearance required extensive human clinical trials.

Figure II.B.1.1
Complexity of Protein Products

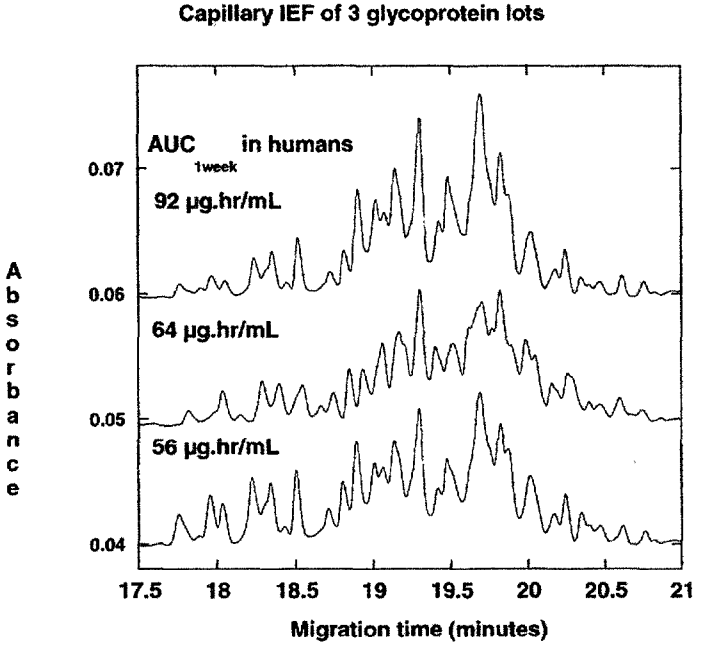
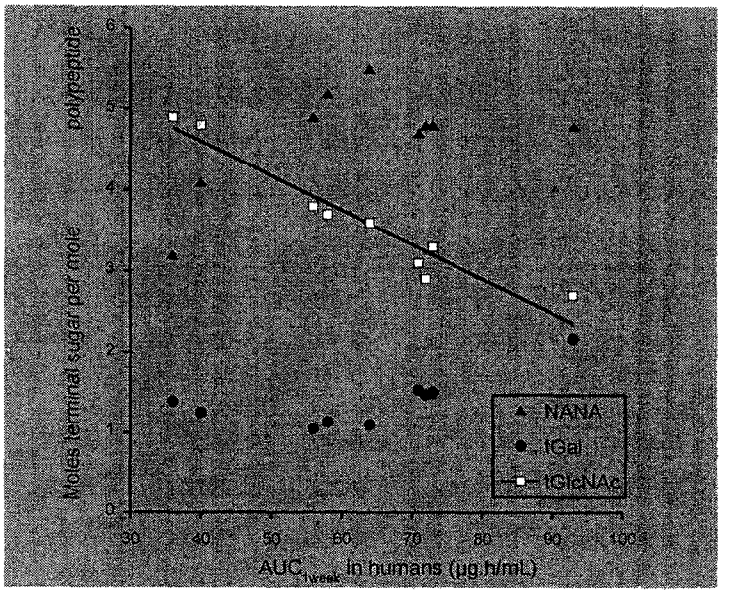


Figure II.B.1.2
Glycoprotein A's Clearance Depends on Terminal GlcNAc



2. Are there new technologies that hold promise for helping to characterize proteins?

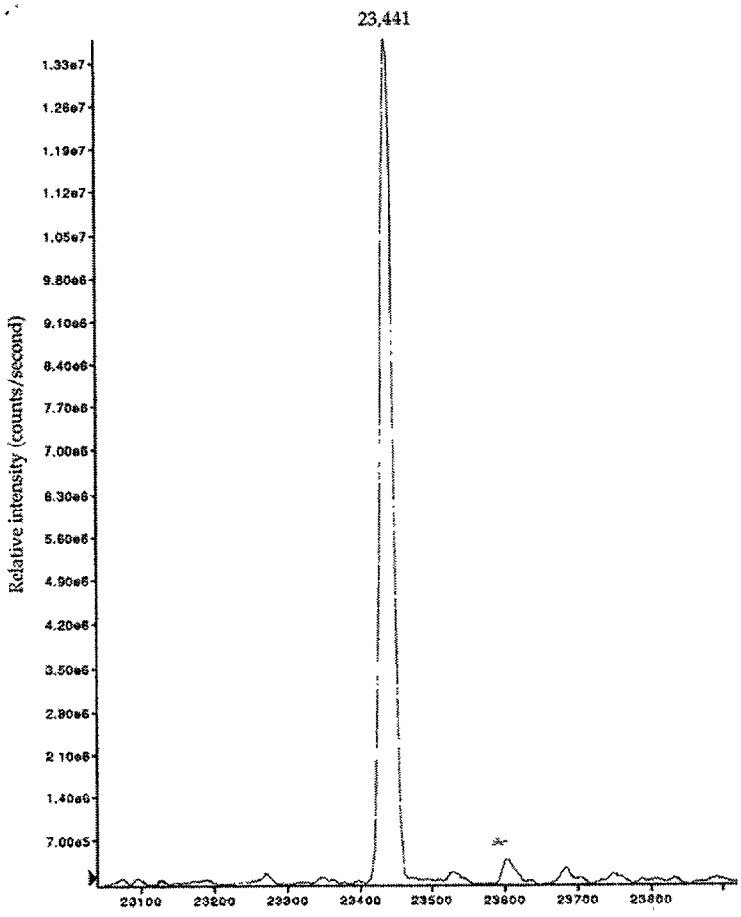
Protein products are composed of a chain of amino acids configured in a specific sequence unique to each protein. Because of the effect of glycosylation, deamidation, or other heterogeneities, the absolute purity of a protein product is extremely difficult to determine. As described in Table II.B.2.1, and Figures II.B.2.1a and 1b, improved analytical technologies may reveal new sources of heterogeneity, but such information is only in the hands of innovator.

Currently, due to the relative structural complexity of protein products, analytical technology cannot bring knowledge of a protein product and its heterogeneity to the same level as for small molecules. Moreover, each protein possesses a unique 3-D structure which dictates its biological activities. A misfolded protein will have altered biological activities leading to altered safety and effectiveness profiles. Three-dimensional structures of proteins cannot be established by standard analytical methods other than x-ray crystallography or NMR. NMR provides an ensemble average structure, with poor sensitivity to low level components, while X-ray crystallography will be a selective assessment of the bulk drug in solution: only identically folded molecules will co-crystallize; misfolded or variant molecules may well be excluded from the crystallization process.

Table II.B.2.1
Improvement of Chromatography Columns

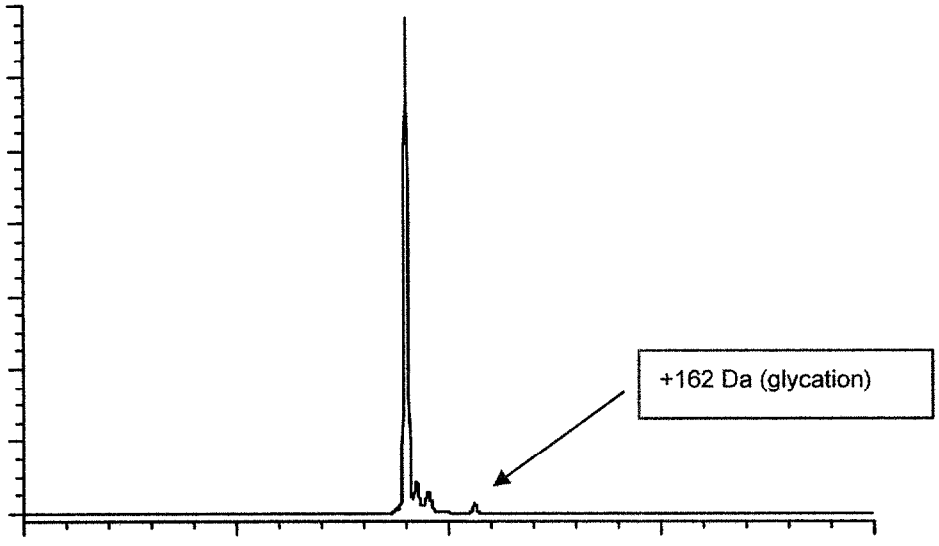
Method	Number of Peaks	Modifications
IND	5	2
Phase III	8	5
Post-approval	10	7

Figure II.B.2.1a
Improved Analytical Technologies May Reveal New Sources of Heterogeneity



* 1997-Mab1 light chain glycated form is hidden in baseline noise (early instrument). By 1999 the technology was developed to clearly distinguish the glycated form.

Figure II.B.2.1b
Improved Analytical Technologies May Reveal New Sources of Heterogeneity



1999–MAb2 Light Chain Glycated Form is Clearly Distinguished (by new instrument).

3. **What factors, including quality attributes, impurity profiles, and changes in the manufacturing process, should be considered when assessing similarity of different protein products?**

The factors to be considered should include cell lines characterization, raw materials controls, process validation and controls, facility and equipment validation and controls, product characterization (structure, purity/impurity profiles, biological activities), relevant safety profiles in animals, as well as PK/PD and relevant safety and effectiveness profiles.

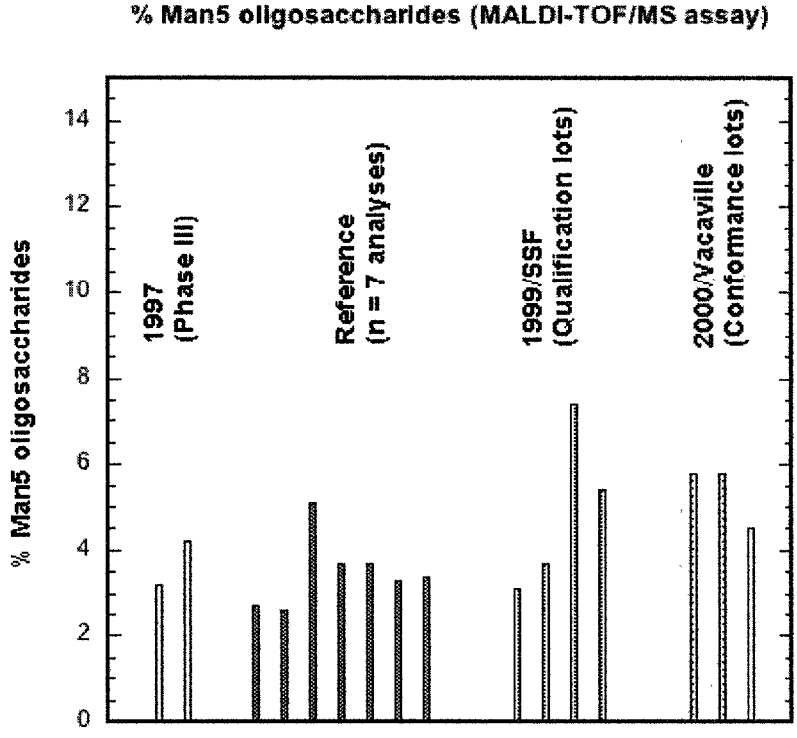
4. **Is it possible to accurately predict safety and efficacy from analytical studies?**

No, it is not possible to accurately predict safety and effectiveness from analytical studies. A follow-on manufacturer will not be using the same cell line, manufacturing process, or procedures as the innovator. Because the process directly affects the characteristics of the follow-on protein product, the probability that the two molecules will have similar safety and effectiveness profiles is unpredictable. As depicted in Figure II.B.4.1, even in the hands of an innovator, with extensive process development and analytical experience, a manufacturing change may result in an unexpected new product characteristic. It is risky to rely on analytical studies to assess the impact of a change to a product and it is even more risky to rely on analytical studies to assess the impact of differences between two products.

In addition, proteins products can be difficult to characterize. The available scientific tools are not sufficiently accurate and precise to adequately detect subtle differences between two molecules. A subtle difference between two products can result in different immunogenicity profiles, or impact the safety and/or effectiveness profile of the products. Furthermore, potency assays typically show only some aspects of biological activity which often are not directly related to a product's mechanism of action. Potency measurement rarely measures effectiveness in man. Consequently, it is unlikely that the follow-on manufacturers could address all the aspects of quality, safety and effectiveness of protein products without reliance on additional data from animal and human studies.

Figure II.B.4.1
Impact of Process Changes during Phase III

- Increase in percent Man5 oligosaccharide
- Mouse PK bioequivalence study was insufficient to resolve this matter
- Could only be resolved by a human PK bioequivalence study
  - Bioequivalence was later demonstrated



C. IMMUNOGENICITY

1. How, and to what extent, should immunogenicity be evaluated for a follow-on protein product?

Immunogenicity should always be evaluated for follow-on protein products. In fact, it has been observed that the initial clinical trial for a new or re-engineered product may or may not identify a correlation between drug immunogenicity and safety-related events, or between immunogenicity and effectiveness loss. Therefore, immunogenicity cannot be reliably assessed until extensive patient studies (Phase III or IV) are conducted, in which patients are treated and followed over a number of years.

A survey of prescribing information for approved therapeutic proteins shows wide variability in their immunogenicity rates, ranging from 0.1% to >50%. There is similarly a wide range in the clinical sequelae associated with immunogenicity, ranging from no consequence, to anaphylactoid responses, to loss of effectiveness, to autoimmune disease. Immunogenicity is also likely to vary with type of disease and the co-medications given to patients. People with autoimmune diseases, for example, may be expected to have a more prevalent immune response to therapeutic proteins than oncology patients who may be on other immunosuppressive drugs. In fact, the immune response may vary across different cancer types due to the specific disease type and the specific chemotherapeutic agents. Consequently, individual patient populations must be separately evaluated for the potential immunogenicity of a drug. A low percentage of seroconverting patients treated for one disease is not predictive of the seroconversion rate in another patient population, or in the same patient population treated with different co-medications.

Studies should explore the link (if any) between adverse reactions or loss of effectiveness, and immunogenicity. One way to achieve this goal is to evaluate patients discontinuing treatment because of loss of effectiveness or safety concerns for the possible presence of anti-drug antibodies. A sufficiently large patient population should be studied to determine the incidence of adverse reactions and loss of effectiveness, and whether these correlated with immunogenicity.

2. **Under what circumstances should comparative immunogenicity studies be conducted?**

Generally speaking, industry uses the word "comparability" to describe studies done on one company's product after changes to the manufacture of that product. In this question, we think FDA is asking whether there should be "comparative" immunogenicity studies, whereby there are head-to-head trials of the innovator protein product and the follow-on protein products to determine whether the immunogenicity profiles of the two drugs are different. Extensive comparative immunogenicity studies should be conducted for every follow-on protein product. Understanding the impact of alternative routes of delivery, doses, and formulations allows the innovator to define a process with optimal manufacturing properties, and a product with a high-safety profile and known immunogenicity. This information would not be available to manufacturers of follow-on protein products.

It is exceptionally difficult to define what is meant by "comparative immunogenicity" since there are so many potential endpoints and means of making comparability measurements. One can measure the percentage of seropositive patients, but that number alone does not indicate whether there is any risk associated with the those cases. More extensive characterization of the immune response is often needed to interpret the biological significance of each case. Such characterization should include the serum titer in seropositive patients, and whether the antibodies alter drug PK or neutralize drug activity. In addition, one could measure the isotype of the antibodies, the maturation of the immune response, binding affinity of anti-drug antibodies, and the ability of those antibodies to cross-react with endogenous "self antigens". Any of these endpoints may, or may not, correlate with adverse events or loss of drug effectiveness. It is impossible to predict which measure is likely to be the most meaningful without an extensive clinical experience, including a panel of analytical measurements designed to characterize the immune response.

The apparent immunogenicity of a drug also depends on the tests used to measure the immune response. In the terminology of a recent FDA-Industry publication on immunogenicity testing (Mire-Sluis et al. 2004), these assays are "semiqualitative," in that there are no standardized reference materials for comparison, and no widely-accepted assay format. The immune response will probably be polyclonal,

and will evolve with time as increasingly high affinity antibodies occur or the immune response wanes as a result of "tolerance" to the drug. Genentech has generated data from anti-drug antibodies in test samples that were detected only when the drug was *indirectly* immobilized on microtiter plates via a drug-biotin conjugate and streptavidin-coated microtiter plates. If the drug was *directly* immobilized on the plastic surface of the microtiter plate, a common practice in the industry, it was always oriented "active site down" and the sample's "in vivo neutralizing antibody" could not be measured. This illustrates the highly technique-dependent nature of the measurements. The fact that different manufacturers would be using different assays confounds comparisons across laboratories and products. Typically multi-lab studies require cross-validation between labs to generate meaningful data.

We occasionally have noted during drug development that various changes to the drug product do lead to apparent increases in immunogenicity in preclinical studies or clinical trials, and have, therefore, avoided the more antigenic forms. This kind of knowledge would not be available to a manufacturer of a follow-on product without the clinical experience gained during drug development.

D. PRECLINICAL AND CLINICAL

1. When and how would it be appropriate to streamline or eliminate certain animal or human studies during development of a follow-on protein product?

In order to evaluate the safety and effectiveness of a follow-on protein product, it is imperative that the appropriate preclinical and clinical studies be conducted. In most cases, clinical studies beyond a "bioequivalence" study will be necessary to determine the safety and effectiveness of the follow-on product.

Assuming that a follow-on protein product is produced by a company without the development experience generated by the innovator, there will be a substantial need for in vitro analytical analyses, preclinical animal studies, and, ultimately, clinical trials to demonstrate that the two products have the same therapeutic effects. Differences that may occur due to an alternative manufacturing process for the follow-on protein include but are not limited to, host cell proteins, aggregation, product-related variants, and endotoxin levels. These differences could lead to atypical PK/PD and/or toxicity profiles.

It would not be scientifically valid to make the assumption that the follow-on protein product will have the same in vivo effectiveness and safety as the innovator's product; therefore, the appropriate animal studies must be performed to determine if the follow-on product is the same as the innovator's product. Once those studies have been completed and have shown that the two molecules are comparable in terms of pharmacologic effects and toxicity, there may be an option to streamline a few of the remaining preclinical toxicology studies, but only with careful guidance from the FDA.

Regardless of the in vitro and preclinical data, there will still be a need to confirm that the innovator and the follow-on protein products have the same therapeutic effects in a human clinical trial. Bioequivalence data alone (PK) is not adequate due to the complex nature of protein products. The manufacture of Raptiva (efalizumab) is a specific example where a manufacturing change impacted the therapeutic effects of the monoclonal antibody. This antibody was originally manufactured by XOMA, Ltd. and used in Phase I/II clinical studies. The manufacturing process was transferred to Genentech to generate material for the Phase III clinical studies. After the transfer of the process to Genentech, analytical and formulation differences were observed; however, these were expected to be inconsequential. Animal studies were performed and suggested that the expected human PK profile would be consistent with the original molecule. However, a human bioequivalence study demonstrated a difference between the XOMA and Genentech material (Genentech product had higher AUC). A subsequent study demonstrated that the formulation alone did not account for the difference. Because of the unexpected PK differences, an additional Phase III study was performed to determine the safety and effectiveness of the Genentech material. The study yielded a surprising result, i.e., the XOMA and Genentech materials did not have the same therapeutic effects—there was a lower PASI response to Genentech's material despite a higher peripheral drug concentration (Barron 2004).

Given the complexity of therapeutic proteins, the impact of changes in PK on safety and effectiveness cannot be reliably predicted either by in vitro analyses or by preclinical animal studies. These data suggest that our current understanding of human biology is not yet at a stage which allows for elimination of animal or human

studies for follow-on protein products. Thus, FDA should require manufacturers of follow-on protein products to conduct controlled clinical trials to clearly establish the safety and effectiveness of their follow-on protein products.

E. POTENCY AND SURROGATES FOR EFFICACY AND SAFETY

1. What factors should be considered regarding bioactivity and potency assays used for comparing two products?

There are four critical factors that must be considered regarding bioactivity and potency assays used for studies assessing the similarity of innovator and follow-on protein products: the nature and availability of critical assay reagents; the knowledge of critical test performance parameters; the ability to establish cross-validation between test laboratories and/or test methods; and the inherent limitations of biological activity assays in distinguishing between various variants of the protein product.

The potency test and other biological activity tests are the proprietary information of the innovator. These tests may involve critical reagents (e.g., binding ligands, cell lines, monoclonal antibodies), some of which may also be proprietary to the innovator. New lots of these critical reagents are typically controlled via internal manufacturing processes, certificates of testing, and SOPs governing changes in lots of reagents used in critical tests. There may be extensive characterization of critical reagents, with important features specified by the innovator. A follow-on manufacturer could develop a test, but it would not incorporate these reagents, nor the knowledge of critical test performance parameters, generated by the innovator during assay development. Consequently, it would not be the same test.

Analytical laboratories in the clinical chemistry, forensic, and environmental industries have established extensive procedures for comparing test laboratories and test methods. Typically these involve extensive cross validation, with multiple blinded samples, to establish that results from two laboratories, or using two methods, give comparable results. Periodic re-certification of laboratory proficiency may also be required. The farther analytical methods move from the purely physical (e.g., NMR spectra, Mass Spectra) to the biological arena, the more difficult these comparisons become. Even between laboratories within the same

company, there are many examples of seemingly unimportant parameters affecting assay results (e.g., the source of the water, the ambient humidity, and temperature, the way in which dilutions are made). Biological assays are inherently more prone to such potentially confounding factors than are the physical assays that are used to characterize small molecule drugs.

Biological activity assays by their nature give a result that reflects an aggregate response to the collection of variants present in a complex protein product. They do not allow one to distinguish among the various subpopulations of the protein product. The aggregate response is not necessarily a linear addition of variants, and not necessarily sufficient to show the similarity of two protein products made by different companies. For example, if 10% of a drug were $1/10^{th}$ as active as the main variant, the potency test would show that the bulk drug was 91% active, within the variability in the assay (i.e., the difference would not be detected). Alternatively, if 10% of the drug were 10-fold more potent, then the potency test would show a 190% activity (i.e., readily distinguished as different by the assay). These two variations give much different readout in the assay, yet they both arise from 10-fold changes in 10% of the material.

2. **What is the role of in vitro and in vivo assays for use as surrogates in establishing safety and effectiveness?**

In vitro assays are not adequate surrogates for safety or effectiveness. The potency test used for lot release tests only one facet of biological activity of the molecule. Ideally this test is related to the expected mechanism-of-action of the therapeutic protein. However, it is not comprehensive (it does not necessarily test all possible mechanisms of action), nor is it related to safety (it is not based on mechanisms of toxicity). The potency test measures lot-to-lot consistency in the manufacturing process from the standpoint of biological activity. Ideally it is sensitive to possible variability in the manufacturing process, as are other controls in the lot release program. For example, carbohydrate structures may have some degree of variation owing to the mammalian cell culture source of the therapeutic protein and these variations could be detected by a biological activity test. In summary, protein products often have more than one biological activity, and the selection of the most appropriate potency assay requires careful consideration of drug's MOA

(mechanism-of-action) relevance, as well as a number of critically important practical issues, including precision, robustness, stability indicating, economic, and others.

This conclusion has been described in published literature and ICH Guidance. For example, Mire-Sluis reported "It has been generally accepted that bioassays are a quality issue and that they should not necessarily need to be designed to predict or reflect any clinical effectiveness per se, as this is the purpose of clinical trials. Bioassays are used almost entirely to demonstrate batch to batch consistency." (Mire-Sluis 2001) Also, ICH Guidance Q6B states "Mimicking the biological activity in the clinical situation is not always necessary. A correlation between the expected clinical response and the activity in the biological assay should be established in pharmacodynamic or clinical studies." (ICH Guideline [Q6B 1999]) As concluded in ICH Q6B, determination of clinical efficacy should be based on the outcome of clinical studies not on biological assays.

F. TERMINOLOGY

1. Please comment on the appropriateness of this notice's working definition of "follow-on protein" as a protein that is intended to be a similar version or copy of an already approved or licensed protein pharmaceutical product

Genentech has no objection to using the term "follow-on protein" as defined by FDA. However, as defined in CDER Orange Book for Approved Drug Products, drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they are expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. We believe that in most cases sufficient analytical tools are not currently available to determine whether a follow-on protein product is a copy (pharmaceutical equivalent) of an already approved or licensed protein pharmaceutical product. According to the proposed definition, a follow-on protein product may be designated as a "similar" version of an already approved or licensed protein pharmaceutical product. Genentech believes demonstrating a follow-on protein product is "similar" to an innovator's product must include the necessary comparative safety and effectiveness studies in animals and humans in addition to analytical studies.

III. CONCLUSION

Again, Genentech appreciates the opportunity to present at the September 14–15 FDA Stakeholder meeting, and to comment more fully to the Docket. We applaud the FDA in its effort to review and address the many and complicated scientific issues raised in the context of developing a regulatory and approval pathway for follow-on protein products. We urge a similar review of the legal issues inherent in a follow-on policy, as the legal and scientific issues are integrally related and relevant to the scope and direction of any such policy.

Genentech looks forward to the upcoming FDA document on how it has treated protein products in the past, to the FDA/DIA Scientific Workshop in February 2005, and to continuing to work with the FDA and other interested parties on these important issues.

Sincerely,

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